PSYCHOSOCIAL PREDICTORS OF ADVERSE EVENTS IN HEART FAILURE:

THE UTILITY OF MULTIPLE MEASURES

by

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ABSTRACT

Title of Thesis: Psychosocial Predictors of Adverse Events in Heart Failure: The Utility of Multiple Measures

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Background and Methods: Approximately 5.7 million Americans experience heart failure. Heart failure is associated with a high rate of hospitalization and has a sizeable economic impact. Numerous physiological risk factors are associated with the onset of heart failure, however evidence suggests that psychosocial factors are important. Depression, stress, and major life events are common in populations with cardiovascular disease, who are likely to develop heart failure, and have all been associated with poorer physical health. Rushton and colleagues' principle of aggregation suggests that averages taken from multiple measurements of psychosocial and other factors may improve predictive power as compared to single measurements. Using a longitudinal design, the aim of the present study was to determine if depression, perceived stress, and major life events predict adverse events (cardiac-related hospitalization or death) in heart failure patients over a maximum long-term follow-up of 36 months. In addition, we aimed to evaluate whether averages taken from multiple measures were better predictors of time to first adverse event than single measures. Similar analyses were conducted using standard predictors of heart failure outcomes, including the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS), KCCQ Symptom Burden Score (KCCQ-SB), KCCQ Total Symptom Score (KCCQ-TS), brain natriuretic peptide (BNP), and the 6-Minute Walk Test (6-MWT). <u>Results:</u> In our sample (n=106), median event-free survival following 3 month assessement was 747 days. Results from unadjusted and adjusted Cox regression survival analyses indicated that no single or average measure of perceived stress, depression, or major life events significantly predicted event-free survival. For the KCCQ, in adjusted analyses, eight of the nine average KCCQ scores (KCCQ-OS baseline and 3 month average, KCCQ-SB baseline and 3 month average, KCCQ-OS clinic visit average, KCCQ-SB clinic visit average, KCCQ-TS clinic visit average, KCCQ-OS all visit average, KCCQ-SB all visit average, and KCCQ-TS all visit average) were significant predictors of CV hospitalization or death, whereas for single measures only KCCQ-OS and KCCQ-SB at baseline were significant. All single and average BNP measures were significant, but all measures of 6-MWT were not. <u>Conclusion:</u> The present results did not provide clear support for the hypothesis that average measures taken from multiple scores were better predictors than single measures. However, for KCCQ scales, there was weak evidence to support this hypothesis. In summary, while psychosocial variables measured in our study were not predictive of event-free survival, BNP, and KCCQ were predictive of event-free survival. Future research on psychosocial predictors in heart failure should examine additional outcomes and utilize a larger sample and more frequent assessments to improve statistical power.

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CHAPTER 1: Introduction

Overview

Heart failure (HF) contributes to significant morbidity, mortality, and economic losses in the United States. Increasingly, there has been an interest in psychosocial contributors to heart failure outcomes. Existing research has examined the role of stress (26; 65; 71), depression (43; 55; 59; 70; 86), and life events (64), in cardiovascular health. However, the evidence is limited and mixed as to whether and which psychosocial factors predict heart failure outcomes (17). In addition, many of the psychosocial studies have been restricted to retrospective studies and cross-sectional data (17).

The present study utilizes a longitudinal design to examine the role of perceived stress, major life events, and depression in heart failure adverse events. Further, we examine whether an average measure derived from repeated measurement of these variables improves the strength of their relationship with adverse events, while also utilizing standard predictors of heart failure outcomes. In this introduction, we will provide an epidemiological overview and definition of heart failure, review the causes and risk factors of heart failure, discuss the role of psychosocial factors - particularly stress, life events, and depression - in cardiovascular disease and heart failure and how these factors may lead to heart failure-related hospitalizations, and consider the utility of repeated measures in improving the reliability of predictors of heart failure outcomes. Finally, we conclude with a summary of our study and a rationale, including research aims and hypotheses.

Epidemiology

Heart Failure impacts 670,000 American lives each year (56) and contributes to significant mortality, with 1 in 9 death certificates (274,601 deaths) in the United States mentioning heart failure in 2009 (29). In total, 5.7 million Americans or approximately 2% of the population currently experience heart failure (69). Frequent hospitalizations and reduced quality of life are common among heart failure patients. In studies of heart failure patients, greater than 50% of patients were readmitted to the hospital within 6 months of discharge (10; 14; 37; 45). The economic impact of heart failure is consequently sizeable and appears to be increasing despite advances in treatment; by 2030, projections estimate that the total cost of HF will increase almost 120% to $70 billion from the 2013 estimated total cost of $32 billion (29; 34).

DEFINITION AND PATHOPHYSIOLOGY

Heart failure is a clinical syndrome which is characterized by reduced cardiac output, increases venous pressures, and is accompanied by molecular abnormalities that cause progressive deterioration of the failing heart and premature myocardial cell death (39). Dyspnea, or shortness of breath, is common among patients with heart failure, and, in part, results from the increased work required to provide oxygen to the congested lungs that have become stiff and inelastic (49).

Heart failure may be classified as systolic or diastolic heart failure. Systolic heart failure is associated with reduced cardiac contractility, whereas diastolic heart failure is associated with impaired cardiac relaxation and abnormal ventricular filling (35). The most common cause of heart failure, and the focus of the present study, is left ventricular (LV) systolic dysfunction (seen in about 60% of patients) (35). Conditions that may be underlying causes of heart failure include coronary heart disease, hypertension, valvular heart disease, chronic pulmonary disease, cardiomyopathy, myocardial infarction, toxin-induced cardiomyopathies (e.g. doxorubicin and alcohol), congenital heart disease, and ischemic heart disease (35; 58). Most cases of LV systolic dysfunction are a result of end-stage coronary artery disease, either with a history of myocardial infarction or with a chronically under-perfused, but viable, myocardium (35). History of myocardial infarction or evidence of coronary artery disease (CAD) is relevant to classifying the etiology of heart failure as ischemic or non-ischemic (21). Ischemic cardiomyopathy is caused by CAD and myocardial infarction and is due to a lack of oxygen damaging the heart muscle (11). Non-ischemic cardiomyopathy, on the other hand, is not related to poor coronary artery blood supply, but to the following four types of heart muscle disease: dilated cardiomyopathy (which may also be related to ischemic cardiomyopathy), hypertrophic cardiomyopathy, and restrictive cardiomyopathy (11).

Development and Risk Factors

Risk factors for heart disease include high blood pressure, high blood cholesterol, diabetes, smoking (89), being overweight or obese, being physically inactive, having a family history of early heart disease, having a history of preeclampsia during pregnancy, unhealthy diet, male sex (89), and female age of 55 or older (57). As a progressive disease, heart failure may begin with the development of atherosclerosis, where fat and cholesterol build up within the artery walls and cause restriction of blood flow (44). Inflammation has been identified as a key pathogenetic mechanism in atherosclerosis (60). Vascular stiffening, endothelial dysfunction, and calcification are additional intermediate markers of heart disease.

Psychosocial Risk Factors and Precipitating Factors

Precipitating factors for frequent heart failure exacerbations are not well understood (17). Existing evidence points to hemodynamic, renal, and/or pulmonary dysfunction, and poor adherence to complex medication and diet regimens as precipitating factors (22; 27; 90). A variety of psychosocial risk factors including lack of social support, depression, and pessimistic outlook may also predict adverse heart failure clinical outcomes (24; 62; 87).

Recently, support has been found for the psychosocial perfect storm conceptual model, which hypothesizes that amplified risk will occur in coronary heart disease (CHD) patients with concurrent stress and depressive symptoms. Alcántara et al. found that over their initial 2.5 years of follow-up, individuals with concurrent high stress and high depressive symptoms had increased risk for myocardial infarction or death relative to those with low stress and low depressive symptoms (3). Of note, individuals with high stress and low depressive symptoms or those with low stress and high depressive symptoms were not at an increased risk of myocardial infarction or death (3). Therefore, it may be important to consider the role of multiple psychosocial predictors in assessing cardiovascular adverse event risk. In this paper, we consider the role that major life events, stress, state and trait anger and anxiety, and depression play in exacerbating cardiovascular hospitalizations.

DEPRESSION AND CORONARY HEART DISEASE

Depression is common among patients with CHD. It is found to be associated with an increased risk of cardiovascular disease (CVD) (46; 61; 72; 88) and of heart failure progression (20; 36; 54; 74; 76; 84). Compared to anxiety or anger, depression was a stronger independent risk factor for adverse cardiac events in a study of patients with cardiovascular disease (CVD) (55). In another study of cardiovascular disease (CVD) patients, depressive symptoms at discharge from a comprehensive 3-month rehabilitation program were a significant predictor of outcome (50). Using the Hospital Anxiety and Depression Scale (HADS-D), it was found that patients with clinically relevant depressive symptoms at discharge had a 2.5-fold increased relative risk of poor cardiac prognosis compared to patients without clinically relevant depressive symptoms, independent of other prognostic variables (50). However, the relationship between depression and adverse events in heart failure may not be so clear; a recent meta-analysis found that major depression, but not mild depression was a predictor of subsequent all-cause mortality in heart failure patients (19)

PERCEIVED STRESS AND CORONARY HEART DISEASE

Perceived stress is the general perception that environmental demands exceed perceived capacity, regardless of source of the environmental demand (65). In a meta-analysis of 6 studies measuring self-reported perceived stress and incident CHD, individuals with high perceived stress were 27% more likely to develop CHD than individuals with low stress (65).

Interestingly, after controlling for sociodemographic, behavioral, and biological risk factors in a population of Hispanic and Latino adult men and women, chronic stress burden – but not perceived stress - was found to be related to a high prevalence of coronary heart disease (odds ratio [OR; 95% confidence interval], 1.22 [1.10-1.36]) (26). The authors of this study concluded that there are advantages to examining multiple indicators of stress in relation to health as the direction and consistency of associations may vary across distinct stress conceptualizations (26). Further, HF patients with consistently high stress levels have been found to have a higher likelihood of cardiovascular hospitalization and death compared to patients with lower stress levels in short-term follow-up (17). This is consistent with an earlier study finding that high stress was associated with a 3-fold increased risk of 30-day all-cause hospital readmission in acute coronary syndrome (ACS) patients, even after controlling for depression and demographic and clinical factors (16). Stress at work and home and financial stress were also reported at a higher prevalence among patients with myocardial infarction, a possible risk factor for heart failure, compared to controls (71). Taking these findings into consideration, it is important to determine whether measures of stress can better predict cardiovascular events when measured repeatedly, potentially yielding a more valid representation of stress over time.

Researchers have also investigated associations between psychosocial stress, as measured by the job demand-control model (JDC), and ischemic stroke and coronary heart disease (CHD). They found that job demands were associated with CHD, but there were inconsistent results in relation to job control (75).

Major Life Events and Coronary Heart Disease

It is hypothesized that there is a link between stressful life events and physical health (83). A longitudinal study provides evidence for the relationship between personal and family-related stressful life events and the onset of heart and circulatory diseases (64). In a cohort with a first myocardial infarction, a known underlying cause of heart failure, stressful life events in the past year were reported more frequently than in an aged-matched control population (71). However, there is a lack of consensus regarding the significance of major life events as a predictor specific to CHD symptoms and events (47; 68; 81; 82).

Rehospitalizations in Heart Failure

Key predictors of heart failure prognosis and rehospitalization include hemodynamic and neuroendocrine dysfunction (72; 79), poor adherence to drug and diet regimens (87), increased symptom perception (32), and health-care seeking behavior (67). In terms of psychosocial predictors, one study found that major life events and social networks did not play an individual role in heart failure hospitalization (68). Optimism, however, was found to be related to fewer heart failure symptoms, improved functional status, and fewer heart failure hospitalizations (86). In a heart failure study of anger and hostility, only hostility significantly predicted all-cause hospitalizations; it did not predict heart failure-related hospitalizations (40). Overall, the role of psychosocial factors as predictors of adverse events in heart failure is still poorly understood (17). Studies are often limited to retrospective analyses of emergency room admissions for HF or to acute laboratory stress studies (2; 51). Further, clear comparisons across cardiovascular studies are obscured by the interchangeable use of psychosocial constructs such as stress and life events.

Reliability, Repeated Measures and Aggregation of Score in Research on Psychosocial Factors and Cardiovascular Disease

While many psychological and behavioral measures may be reliable in the short term, repeated measurement of certain psychosocial variables may improve prediction of outcome variables (18). There is inevitably some error associated with measurement, which may explain the many null findings in behavioral development and personality psychology research (73). The principle of aggregation, as described by Rushton and colleagues, states that the sum of a set of multiple measurements is a more stable and representative estimator than any single measurement (73). Similarly, in the area of personality research, Epstein (18) has used a variety of studies to demonstrate that aggregating behavior over situations and/or occasions can cancel out incidental, uncontrollable factors relative to experimental factors and increase reliability, generality, and replicability of the findings. In the area of stress research, work on cardiovascular reactivity by Kamarck and colleagues found that aggregated scores are associated with enhanced short-term reliability (38). Research in the area of stress and cardiovascular disease may benefit from this approach.

The reliability of stress, depression, and life event assessments may be enhanced by averaging across tasks and test sessions, which could minimize idiosyncratic contribution of individual measurements and best exploit "trait" characteristic effects that contribute to overall scores (38). A measure is considered reliable when it is consistent or stable across time and settings (38). Questions remain as to the optimal number of assessments needed to reliably predict outcomes in the long term. For example, one study found that CHD patients who were identified as moderate to high risk of depression at baseline continued to have higher levels of depression and anxiety and lower levels of wellbeing and social support compared to those at "no to low" risk of depression over a 12-month period (77). Ski and colleagues concluded from this study that the simple screening tool that they used at baseline to identify depression in hospital patients with CHD was effective and had sufficient predictive validity (77). By contrast, others have found increased predictive validity when using measures from multiple time points as opposed to single measures (43). The present study will add to the literature on the utility of repeated measures in cardiovascular behavioral medicine research. We will examine whether the aggregation of multiple measures of stress, major life events, and depression more strongly predicts adverse outcomes in heart failure compared to single measures. Further, we will also analyze whether the multiple measures are more predictive of adverse events than single measures using standard predictors of heart failure outcomes including KCCQ, Brain Natriuretic Peptide (BNP), and 6-Minute Walk Test (6-MWT).

Summary, Rationale, and Aims

Heart failure represents a significant burden to the United States health system with heart failure hospitalizations costing billions of dollars annually. Evidence from the literature linking stress, major life events, depression and cardiovascular health is mixed regarding the role of these variables in heart failure outcomes. Perhaps one of the reasons for these inconsistent results is the fact that studies often rely on the measurement of these variables at only a single time point. Therefore, it is not known whether using multiple assessments of these psychosocial will enhance their predictive value over single assessments. There is still a lack of consensus regarding the predictive ability of these psychosocial variables in determining heart failure-specific outcomes, including hospitalizations and death. Further, it is unknown whether a single psychosocial measure or multiple psychosocial measures are needed in order to best predict adverse heart failure outcomes.

Therefore, the purpose of this study is to determine whether perceived stress, major life events, and depression predict heart failure and cardiac hospitalizations and death. Further, by using both a single measure of these predictors and an average measure of the predictors taken a maximum of five times between baseline and 3 months, we assess whether multiple measures are more reliable in predicting heart failure adverse events than single measures. To assess the "proof of principle," we will also employ single and average measures of standard predictors of heart failure outcomes (KCCQ, BNP, and 6-MWT) in our models.

Specific Aim 1

The first aim of this study is to examine the relationship between perceived stress, depression, and major life events, to adverse outcomes in heart failure. Outcomes assessed will consist of cardiac related hospitalizations and death. Perceived stress will be measured by the Perceived Stress Scale. Major life events will be measured by the Major Life Events Scale. Depression will be measured with the Beck Depression Inventory.

Hypothesis 1

We hypothesize that perceived stress, major life events, and depression will predict heart failure and cardiac hospitalizations and death.

Specific Aim 2

The second aim of this study is to explore the extent to which any relationships attained would be stronger when using averages of multiple measures of standard and psychosocial predictors of heart failure adverse events as opposed to single measures of the predictors at either baseline or 3 months.

Hypothesis 2a

We hypothesize that relationships between perceived stress, major life events, depression and cardiac related hospitalizations and death will be stronger when using a computed average of multiple predictor measures compared to a single predictor measure at baseline or 3 months.

Hypothesis 2b

We hypothesize that relationships between standard predictors of heart failure outcomes (heart failure symptoms, 6-Minute Walk Test [6-MWT], brain natriuretic peptide [BNP]) and adverse events will be stronger when using a computed average of multiple predictor measures compared to a single predictor measure at baseline or 3 months.

CHAPTER 2: Methods

Overview

The methods described here have been adapted from the BETRHEART study protocol. This study employs a longitudinal analysis of the predictive value of perceived stress, major life events, and depression measures for time to subsequent death, cardiac and heart failure hospitalizations.

Study Participants

150 study participants were recruited at the Heart Failure Clinic of the University of Maryland Hospital in Baltimore, MD. Included participants had a current diagnosis of heart failure (left ventricular ejection fraction of ≤ 40% and a New York Heart Association [NYHA] functional status of II-IV for at least 3 months), were in stable condition, and older than 21 years (to represent the majority adult heart failure population). Excluded participants met at least one of the following criteria: (1) documented myocarditis, 2) clinically significant mitral valve disease, 3) thyroid dysfunction 4) current alcohol abuse or abuse within the last six months, 5) implanted left ventricular assist device, 6) prior heart transplantation, 7) active cancer treatment, 8) living in a nursing home, or 9) cognitive impairments interfering with consent and understanding of study materials. All participants included in the present study had completed the basic demographic information packet at baseline and pertinent psychosocial variable measures at baseline, 3 months, and one or more intermediate phone assessments (with the exception of the Beck Depression Inventory, which was only administered at baseline and 3 months). Further, included participants in the present study did not have any congestive heart failure (CHF) or cardiac events between baseline

and 3 month assessment and continued in the study beyond 3 months in order to determine whether or not they had died or had any cardiac or HF hospitalizations (subsequent to the measurement of predictor variables between baseline and 3 months).

MEASUREMENTS

Psychosocial Variables

Beck Depression Inventory (BDI)

Depressive symptoms were measured using the Beck Depression Inventory-II (8). Each of the 21 items in the scale lists four statements arranged in order of increasing depression severity. Greater depressive symptomatology is indicated by higher scores on the BDI-II. Mild depression scores range between 14-19, moderate is between 20-28, and severe is a score of 29 and above (8). The BDI-II is an extensively used and well validated measure (66) with a high internal consistency (0.86 to 0.88 among psychiatric patients and 0.81 with non-psychiatric participants) and previous use in HF patient populations (30). Unlike the questionnaires for PSS and MLE, the BDI-II was only administered during baseline and 3-month follow-up visits. However, consistent with these measures, the BDI also has a recall period of two weeks.

Perceived Stress Scale (PSS)

The 10-item Perceived Stress Scale (PSS) is a reliable and valid measure (12; 13) of the generalized perception of stress over the past two weeks and captures the extent to which an individual believes that life events are stressful or out of control (17). The PSS has been previously used to measure stress in behavioral, epidemiological, and clinical research in diverse populations (5; 9; 12; 13; 28). Total PSS scores range from 0 to 40, with higher scores representative of a perception of greater psychosocial stress.

Major Life Events (MLE)

In the present study, an ad hoc 7-item questionnaire of major life events was created and used during patient bi-weekly phone interviews. Patients were to indicate (yes or no) whether they had any major life events in their family, job/work, finances, health, friends, and other areas of life in the past two weeks. The events in any category could be either positive (e.g. a family member got married) or negative (e.g. a patient recently lost their job) and were counted the same way. In addition, participants were also asked whether or not they have been feeling reasonably happy, all things considered. Each item was scored with a 0 or 1, with 1 indicating that the participant experienced at least 1 event in a given area of life (i.e. family, health, etc.). If participants responded that they experienced an event in a particular area, they were given the opportunity to provide a description of the event(s) in free response format. For the final item, participants who have been feeling reasonably happy also received 1 point. In the present study, an MLE summary score was calculated using only the first six items. Higher scores mean that the participant reported more major life events. Scores therefore could range from 0 to a maximum of 6.

Standard Predictors of Heart Failure Adverse Events

For the second aim of the study, an analysis was conducted to explore the relationship between standard predictors of heart failure outcomes and time to first adverse event following 3-month assessment. These predictors included the Kansas City Cardiomyopathy Questionnaire (KCCQ), brain natriuretic peptide (BNP), and the 6-Minute Walk Test (6-MWT). KCCQ was assessed in all participants and BNP and 6-

MWT was assessed in a majority of participants at baseline and 3-month clinic visits and up to 5 total clinic visits in a subset of the sample who reported high (PSS $\geq$ 15) or low ($\leq$ 9) stress levels.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a 23-item validated scale used to measure symptoms and HF health status (31) and asks patients to report the extent to which they were limited by HF over the past two weeks. Subscales assess HF symptoms, HF physical and social limitations, self-efficacy, and quality of life. The KCCQ has predicted HF exacerbations and mortality (33; 78). As such, we included the KCCQ as a predictor as a means of validating our statistical model. In the present analysis, we examined both the KCCQ summary score (KCCQ-summary), the KCCQ total symptom score (KCCQ-total symptoms), and the KCCQ subscale score of symptom burden (KCCQ-symptom burden) and their relationship to time to first adverse event. We hypothesized that the KCCQ-summary, KCCQ-symptom burden, and KCCQ-total symptom scores would predict time to first adverse event after 3-month assessment.

B-Type or Brain Natriuretic Peptide

B-type or Brain natriuretic peptide (BNP) is a peptide synthesized primarily in the heart and is responsible for mediating the natriuretic and diuretic response (53). In healthy individuals, circulating levels of BNP are normally very low (41). While multiple structural and functional cardiac abnormalities lead to the release of BNP in excess of baseline levels, common triggers among patients with chronic heart failure include left-ventricular systolic and diastolic dysfunction, pulmonary artery hypertension, abnormal right-ventricular size and function, valvular heart disease, and heart-rhythm abnormalities

(53). In particular, volume overload and resulting myocyte stress are common precursors for natriuretic peptide gene expression and a substantial percentage of BNP release (53). BNP is sensitive to a broad range of cardiovascular derangements, such as increased filling pressure (53). As BNP is the current gold standard biomarker for prognosis in chronic HF (53), we hypothesized that it would predict time to first adverse event after 3-month assessment. In this study, we used the natural log of BNP (lnBNP) in our analyses, as is commonly done in the literature.

Six-Minute Walk Test (6-MWT)

Finally, the 6-MWT, developed by Balke and colleagues (7), measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface (4). Participants in the 6-MWT are to walk as far as possible in six minutes at their own pace, taking breaks if needed (4). The 6-MWT has demonstrated utility as a univariate predictor for all-cause hospitalization/mortality and all-cause mortality in patients with systolic heart failure (23). A 6-MWT distance of ≤300 meters has been found to be a simple and useful prognostic marker of subsequent cardiac death in patients with mild-to-moderate heart failure (6). We hypothesized that 6-MWT would predict time to first adverse event after 3-month assessment.

Adverse Events: Hospitalizations for HF, CV Causes, and Death

Patient self-reported hospitalizations were checked against medical records to verify hospitalizations. In the BETRHEART study, hospitalizations were classified as HF-related, cardiovascular (CV)-related, or non-CV related. In this analysis, only heart failure and CV-related hospitalizations were analyzed. HF hospitalizations were defined as hospitalizations where the primary diagnosis was a HF exacerbation related to pump failure or fluid overload. Diagnoses of angina, myocardial infarction, ischemia, or arrhythmia were included under CV-related hospitalizations. Deaths were also included as an adverse event type in the present study.

Procedures

During a routine follow-up visit to the Heart Failure Clinic of the University of Maryland Hospital in Baltimore, MD, potential study participants were identified by a physician and approached by the research team regarding their interest in participation. One of the studies' primary investigators screened for inclusion and exclusion criteria following informed consent. If eligibility was confirmed, participants completed a packet of questionnaires which included the Beck Depression Inventory (BDI), Perceived Stress Scale (PSS), and Major Life Events (MLE) checklist. A blood sample and measurements of current height, weight, and blood pressure were also obtained by a member of the research team. Patient contact information was also collected and follow-up phone interviews were scheduled. Following baseline, interviews were conducted every two weeks for the initial 3-month study period. After three months, follow-up interviews occurred every six months for up to 36 months or until the patient was lost to follow-up, withdrew, or died. These interviews were used to obtain information regarding current health status and cardiovascular events that occurred. Participants were questioned about all hospitalizations and/or procedures that they had undergone in the previous six months and their current symptoms were also inventoried.

Data Analysis

SPSS Statistics Version 22.0.0 (IBM, Chicago, Illinois) was used for data analysis. The primary analytic strategy employed Cox regression analyses and was informed by the research model shown in Figure 1. Separate Cox regressions were used to evaluate the relationship between perceived stress, major life events, and depression and time from 3-month assessment to first adverse event. The same model was also used to evaluate the relationship between the standard predictors (BDI, PSS, and MLE) and time to first adverse event. The sample analyzed contained only participants who did not have any CV or HF hospitalizations between baseline and 3 month assessments.

In addition, SPSS was also used for Kaplan-Meier analysis on select predictor variables (BDI at 3 Months, BDI Baseline and 3 Month Average, PSS at 3 Months, PSS Phone Assessment Average, KCCQ Overall Score at 3 Months, KCCQ Overall Score All Visit Average, lnBNP at 3 Months, and lnBNP All Visit Average). Kaplan-Meier analysis along with log-rank tests were used to determine if there were significant differences between individuals in the three different tertile groups (i.e., low, middle, and high scorers) for predictor variables and event-free survival. Median survival time was also derived from the Kaplan-Meier output.

Covariates

The following known predictors of HF adverse events (assessed at baseline) were selected a priori and added to the statistical models: age, sex, body mass index (BMI), household income (as an index of socioeconomic status), NYHA classification, ejection fraction, creatinine levels, and history of hypertension. For household income, 1 participant was missing data (N=105) and for creatinine, 3 participants were missing data (N=103). Missing data were imputed using the mean of the sample.

Exposure and Outcomes

The exposure variables include total PSS score, total MLE score, and total BDI score. PSS and MLE variables were measured up to seven time points (baseline, phone interviews 1-5, and at 3 months). The BDI was measured twice, at baseline and 3 months. All participants had data at both baseline and 3 months. To compare whether multiple measures of the exposure are more reliable than a single measure, the scores at 3 months are compared to an average of the five scores taken at the five phone assessments (PA). If a score was missing for a participant at one of the 5 assessments, the mean was calculated using as many assessments as were available (e.g. if a subject missed one of the 5 assessments, the average score was taken using the available 4 scores). For the analyses with standard predictors for aim two exposure variables included the following scores at both baseline and 3 Months: KCCQ Overall Summary Score, KCCQ Symptom Burden Score, KCCQ Total Symptom Score, lnBNP, and 6-MWT. In addition, for these standard predictors, three average scores were calculated to be used as exposure variables: Baseline and 3 Month Average, Clinic Visit Average, and Baseline, Clinic Visit and 3 Month Combined Average. The outcome variable was time to first adverse events (which included death, heart failure hospitalization, and cardiac hospitalization, and was dichotomized as: 0=no adverse events occurred after the 3-month assessment; 1=at least one adverse event occurred after the 3-month assessment).

Time to Events

In our Cox regression survival analysis, participants were censored based on their event status, with participants having an adverse event (HF or Cardiac Hospitalization or Death) assigned a value of “0,” and participants never having an event assigned a value of “1.” For all participants, a time to event was calculated. This time to event was calculated as the number of days after the 3-month assessment until the first adverse event occurred for patients with an event, or the number of days after the 3-month assessment that patients remained in the study (i.e. the date of final data collection) for patients that did not have any event.

Power Analysis

Power analyses were conducted with PASS Version 12. Assuming alpha = .05, a 2-tailed test, a standardized predictor variable (SD = 1), a sample size of 106, and an event rate of .53, the study had power = .61 to detect a regression coefficient of 0.3 (corresponding to a true hazard ratio of 1.35 in the population), power = .85 to detect a regression coefficient of 0.4 (a HR of 1.49) in the population, and power = .96 to detect a coefficient of 0.5 (a true HR of 1.65 in the population).

CHAPTER 2: Results

Sample Characteristics

The BETRHEART study originally consisted of 150 recruited participants at the University of Maryland Medical Center and Baltimore Veterans Affairs (VA) HF clinic. A subset of these participants withdrew immediately after consent (n=6) or only had baseline data (n=4), leaving 140 participants in the sample. Further, a few participants died (n=3) prior to completing an assessment at 3 months. In addition, participants without an assessment at 3 months (n=11), who had a CHF or cardiac adverse event before 3 months (n=16), or who withdrew or were lost to follow-up after their 3 month assessment (n=4) were also excluded. The final sample of 106 participants consisted of a group of patients who did not have any HF or CV events prior to the 3 month assessment. This group was further classified as having a CV or HF-related hospitalization or death (i.e. a censored value of 0) or not having any adverse events subsequent to the 3-month assessment for remainder of the study (i.e. a censored value of 1). Figure 2 is a flow chart summarizing the sample selection.

Demographics

In our sample (n=106), participants were an average of 57.6 years old (SD= 10.46 years), and ranged from 34.24 to 81.96 years. The study was comprised of mostly male (n=83, 78.3%) participants and African Americans (n=74, 69.8%). Thirty-one individuals identified as Caucasian (29.2%) and 1 individual identified as American Indian/Alaska Native (0.90%). Most participants (n=105, 99.1%) were not Hispanic or Latino. The sample was predominantly of low socioeconomic status, with about one third of individuals living on less than $15,000 per year (n=37, 34.9%). Twenty-nine individuals had an income of $15,000-$30,000 per year (27.4%), with the remaining 31 (29.2%) and 9 (8.5%) individuals earning between $30,000-$70,000 per year and over $70,000 per year, respectively. In addition, most participants were either disabled (n=59, 55.7%) or retired (n=23, 21.7%) and had a history of smoking (n=76, 71.7%) and hypertension (n=83, 78.3%). Mean BMI fell in the obese range at 31.7 (SD=7.85) and ranged from 17.85 (underweight) to 52.31 (obese). The majority of participants had mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity, falling into NYHA Class II (n=64, 60.4%). Table 1 and Table 2 provide additional details on sample characteristics.

Time to Events

For our total sample, median survival following 3 month assessment was 747 days. Among those participants having an adverse event after 3 months (52.8%), the median time to event was 270.50 days. Among the participants not having any adverse events after 3 months (47.2%), the median follow-up time (before being lost due to lack of response, withdrawing from the study, or completing the study) was 1049.50 days. These results are also included in Table 1.

Psychological Scale Scores and Interrelationships

Summary statistics for the stress, depression, and major life event variables are shown in Table 3. In general, predictor variables were highly correlated with each other as shown in Table 4. Predictor scores that were taken more closely together in time also tended to be more strongly correlated than two predictor scores taken at two points further away in time from one another.

Aim 1

The first study aim was to examine the relationship between perceived stress, depression, and major life events, to time to first HF or CV hospitalization or death following 3 month assessment. Table 5 shows the results from unadjusted and adjusted Cox regressions for psychosocial predictor variables of interest (perceived stress, depression, and major life events) and time to adverse events (HF or CV hospitalization or death). As this table shows, none of the stress, depression, or major life event variables could significantly predict the time to first adverse event following 3 month assessment. An example analysis demonstrating effects of covariates using the average of PSS measures from all available phone assessments (PSS PA Average) as a predictor is provided in Table 6 to demonstrate this finding. Of note, across all analyses, creatinine was consistently the only significant covariate. In this example analysis, the hazard ratio and p-value for creatinine is 2.888 and p=.001.

In addition, Kaplan-Meier curves (Figure 3, Figure 4, Figure 5, Figure 6) present time to first adverse event among individuals scoring in the low, moderate, and high tertiles for select psychosocial variables: BDI at 3 months, BDI average (the mean of baseline and 3-month BDI) PSS at 3 months, and PSS phone assessment average. For BDI, there are no significant differences between the tertile groups (Figure 3, [X^2=3.407; df=2; p=0.182] and Figure 4, [X^2=4.894; df=2; p=0.087]). For PSS measures in Figure 5 (X^2=0.014; df=2; p=0.993) and Figure 6 (X^2=0.016; df=2; p=0.970), log rank tests again confirm that there is no significant difference between the tertile groups for time to first adverse event; this is reflected visually by the overlapping lines in these graphs.

However, there is a pattern of results where individuals scoring in the middle tertile for the BDI are least likely to experience an adverse event, individuals scoring in the top tertile on the BDI are most likely to experience an adverse event, and the bottom tertile of BDI scorers are in between.

AIM 2

The second study aim was to determine whether an aggregate average predictor score could predict time to an adverse event better than a single predictor score. Examining the results from the survival analyses in Table 5, none of the aggregated average psychosocial scores (depression, perceived stress, or major life events) significantly predicted time to adverse event in any of our analyses. Furthermore, there was no evidence that the use of an aggregate average score tended to show a stronger relationship with events compared to the use of a score at baseline or 3 months alone.

Single vs. Aggregated Relationships for Known Heart Failure Predictors

We next examined known predictors in order to assess the "proof of principle" regarding the enhanced predictive value of multiple versus single assessments in heart failure. We assessed whether multiple assessments were superior to single assessments as predictors using the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Score, KCCQ Symptom Burden Score, KCCQ Total Symptom Score, Brain or B-Type Natriuretic Peptide (BNP), and the 6-Minute Walk Test (6-MWT) and time to first adverse event after 3 months as the outcome.

Analyses (Table 7) indicated that that the KCCQ Overall Score and Symptom Burden Scores at baseline, 3 months, and taken as averages are all highly correlated with each other; for this reason, separate regressions were run for each of these predictors. Results of adjusted analyses show that two of six single KCCQ measures were significant predictors, while eight of nine average KCCQ measures were significant predictors. Both baseline and 3 month average KCCQ Overall Summary Score (Exp(B)=0.984, 95% CI: 0.962-.998, p=0.029) and baseline and 3 month average KCCQ Symptom Burden Score (Exp(B)=0.982, 95% CI: 0.966-.997, p=0.022) significantly predicted time to first adverse event. Baseline KCCQ Overall Summary Score (Exp(B)=0.984, 95% CI: 0.969-.999, p=.042) and baseline KCCQ Symptom Burden Score (Exp(B)=0.987, 95% CI: 0.975-.999, p=.030) significantly predicted time to adverse event, while the 3 month KCCQ Overall Score (Exp(B)=0.982, 95% CI: 0.964-1.001, p=.058), did not. KCCQ Total Symptom Score clinic visit average (unadjusted: Exp(B)=0.983, 95% CI: 0.970-.997, p=.017; adjusted: Exp(B)=0.981, 95% CI: 0.965-.997, p=.023) and the average of all visits (unadjusted: Exp(B)=0.982, 95% CI: 0.968-.996, p=.015; adjusted: Exp(B)=0.981, 95% CI: 0.964-.998, p=.030) significantly predicted time to first adverse event in both unadjusted and adjusted analyses, as well.

Notably, KCCQ clinic visit and all average scores for Overall Summary Score, Symptom Burden Score, and Total Symptom Score, were all significant in unadjusted and adjusted analyses. The results of the unadjusted and adjusted regressions are shown in Table 8. As Table 8 shows, some KCCQ predictors significantly predicted first adverse events in unadjusted analyses, but these results were no longer significant once the covariates were added to the model.

Kaplan-Meier curves are also provided for KCCQ Overall Score at 3 months (Figure 7, [X2=1.865; df=2; p=0.394]) and KCCQ Overall Score all visit average (Figure 8, [X2=4.168; df=2; p=0.124]). While log rank tests do not show any significant differences between the tertile groups for these predictors, visual comparison of the graphs reveals a trend among the tertiles for KCCQ Overall Score all visit average as compared to the KCCQ Overall Score at 3 months; curves in the graphs for KCCQ Overall Score all visit average are relatively more discrete and show a trend that the lower an individual's all visit average KCCQ Overall Score (lower scores indicate poorer health), the more likely they were to experience a first adverse event.

For BNP, baseline, 3 month, baseline and 3-month average, clinic visit average, and all visit average were also all significant predictors of first adverse event (Table 9). The lowest adjusted hazard ratio was with BNP at 3 months (Exp(B)=1.527, 95% CI: 1.181-1.974, p=.001); the highest was with the baseline, clinic visit, and 3 month combined average (Exp(B)=1.775, 95% CI: 1.290-2.442, p=.000). Results of the adjusted and unadjusted Cox regressions are summarized in Table 9. Kaplan-Meier curves (Figure 9 and Figure 10) for BNP at 3 months (X2=14.372; df=2; p=0.001) and BNP all visit average (X2=16.069; df=2; p=0.000). Corresponding log rank tests show that there are significant differences between BNP tertile groups and probability of first adverse event. The graphs show that the higher an individual's BNP, the more likely that individual is to experience a first adverse event.

Lastly, in the unadjusted regressions, the 6-Minute Walk Test (6-MWT) at 3 months (Exp(B)=.999, 95% CI: .998-1.000, p=.041), the baseline and 3 month average (Exp(B)=.999, 95% CI: .998-1.000, p=.026), the clinic visit average (Exp(B)=.999, 95% CI: .998-1.000, p=.029) and the all visit average (Exp(B)=.999, 95% CI: .998-1.000, p=.026) all significantly predicted time to first adverse event. However, these predictors did not remain significant in the adjusted analyses. Results of these regressions can be found in Table 10.

CHAPTER 4: Discussion

SUMMARY OF FINDINGS

The purpose of the present study was to examine the relationship of perceived stress, depression, and major life events, to adverse events in heart failure over a follow-up period of 36 months. In addition, we explored the extent to which relationships obtained would be stronger when using averages of multiple measures of standard and psychosocial predictors as opposed to single measures of the predictors. To further explore this hypothesis, we compared single with average measures (obtained from multiple assessments) using standard heart failure predictors.

Results of this study do not support the hypothesis that perceived stress, major life events, and depression are associated with time to first adverse event in heart failure patients over 36 months of follow up. Only major life events trended toward significance. However, the direction was opposite of what was hypothesized. For these psychosocial variables, the present data also did not indicate that average scores had more predictive power than scores taken at a single time point (baseline or 3 months) only.

However, creatinine, BNP (both single and average measures in all unadjusted and adjusted analyses), and select KCCQ scores were significant predictors of event-free survival in this sample. Results of the analyses for BNP and KCCQ scores provided only weak support for our hypothesis that multiple measurements would be superior to single measurements. With respect to the 6-MWT, neither single nor average measures single and average measures were significant predictors in any adjusted analyses.

AIM 1

Our study of heart failure patients did not show a statistically significant relationship between perceived stress, major life events, and depression and an increased risk of having a first adverse event during the study period.

The lack of a relationship between depression and events is surprising given prior research in this area (24; 42), which demonstrated that increasing levels of depression are predictive of mortality and rehospitalizations in HF patients. Regarding depression, it is important to note that the mean BDI scores in this study decreased from 11.68 at baseline to 8.67 at 3 months. For the BDI-II used in the present study, these mean scores correspond to minimal depression based on BDI guidelines. However, our findings may be consistent with a previous study that found no significant difference in mortality and hospitalization in patients with mild versus no depression (36). A meta-analysis of nine studies with 4012 heart failure patients also found that major depression, but not mild depression, was a predictor for subsequent all-cause mortality after heart failure (19).

As our BDI Kaplan-Meier curves show, there appeared to be some overlap between the first two BDI score tertiles, while the highest BDI tertile trended toward an increased likelihood of having a first adverse event. In the aforementioned study (36), an association was only found between major depressive disorder (scoring 10 or higher on the BDI and a positive National Institute of Mental Health Diagnostic Interview Schedule screening) and increased mortality at 3 months and increased hospital readmission at 3 months and 1 year (36). The relative minority of our sample falling in the highest tertile of BDI scores (scores ranging from 10-36 for BDI at 3 months) may explain why no effect on time to first adverse event was found for BDI. The range of the scores for this highest tertile is large, and includes a diverse group of individuals with both minimal depression and individuals with severe depression. With a relatively non-depressed sample, any effect of depression on adverse events may have been undetectable. Finally, it is important to note that it appears that the severity of our sample's depressive symptoms significantly ($t=-5.36$, $p=0.000$) decreases from baseline to 3 months, indicating that participants are overall becoming less depressed with time. This may be another reason why depression was not a significant predictor in our study.

Another issue may be characteristics of the present sample. Compared with the previous meta-analysis, where the mean age across the nine studies was 69.91, our sample is notably younger, with a mean age of 57.64. Depression may therefore be a more important predictor in older populations as compared with younger populations. In addition, whereas our sample was predominantly African American (69.8%), the studies evaluated in the meta-analysis were international with six of the nine studies coming from either Europe or Asia. Relatively few patients in these studies were likely to be African American. When the three included studies from the United States were more carefully examined, two reported race (1; 70); in this pair of studies, the samples were predominantly white (72.35-86%). The significant findings for depression and heart failure events in the literature may therefore not be generalizable to our study sample.

While a previous study showed that high stress scores measured every 2 weeks were associated with a higher likelihood of short-term CV hospitalization or death in the BETRHEART population, these findings were based on short-term analysis of data collected every two weeks for three months, with a subsequent follow-up of 6 months. The longer follow-up used in our study may suggest that an initial measure of perceived stress may be a less salient predictor of hospitalizations and death over extended periods of time in this population. Furthermore, the PSS (as well as the MLE checklist and BDI) asks participants to recall their stress in the previous two weeks. Since the frame of recall is only 2 weeks, responses may not be able to predict adverse event outcomes that follow months, or even years, later.

Contrary to our hypothesis, no single or average measure of major life events was related to a higher likelihood of having a first adverse event among heart failure patients. One of the reasons for this may be related to the way major life events were measured in this study. The ad-hoc checklist for major life events captured both positive and negative life events and allowed respondents to decide whether or not something should be considered a major life event. As such, a major life event such as a participant's granddaughter moving so that she could begin working at a "fancy restaurant" (as one participant wrote) was counted the same as a participant's sister being arrested and the participant needing to help her "get out of jail" (also noted by another participant). We were unable to separate out positive and negative life events as any indicator of the nature of the event was limited to brief qualitative statements made by respondents if they answered positively that they had experienced an event in a particular domain (such as family, financial, etc.). Overall, use of MLE scores was limited by the fact that these scores were constructed from a checklist created for our study for another purpose—that is, to rule out seriously life events in our analyses of other variables.

In the context of the literature previously reviewed, our findings are consistent with a general lack of consensus regarding the significance of major life events as a predictor to CHD symptoms and events (47; 68; 81; 82). We previously mentioned one study that found a link between stressful life events and the onset of heart and circulatory diseases (64). It is important to note that, in this study, participants were asked about life events in the preceding month, and follow up was six months. By contrast, our study asked participants to recall life events in the past two weeks, and follow-up was three years. A longer frame of recall may help improve the predictive value of major life event scales used to forecast events in long-term follow up. Furthermore, while life events may be involved in the initial onset of cardiovascular diseases, their role in exacerbating adverse events in the long-term once disease has progressed remains unclear.

AIM 2

Our results do not support the hypothesis that perceived stress, depression, and major life event average scores taken from multiple assessments predict the likelihood of first adverse event better than scores at baseline or 3 months alone. On one hand no single or average stress, depression, major life event, or 6-MWT scores significantly predicted likelihood of first adverse events. By contrast, for the KCCQ, all but one KCCQ average score (KCCQ-TS baseline and 3-month average was not significant in adjusted analyses) significantly predicted time to first adverse event. At the same time, only two single KCCQ measure, KCCQ-OS baseline and KCCQ-SB baseline were significant predictors in adjusted analyses. All BNP single and average scores significantly predicted likelihood of first adverse event. For BNP, while all scores were highly significant predictors, hazard ratios were only slightly larger for average BNP values compared to BNP values at either baseline or 3 months. In sum, the findings for KCCQ and BNP taken together, provide weak support for the hypothesis that, in the long term, multiple average measures predict adverse events in heart failure patients better than single measures.

Although average psychosocial variables and 6-MWT were not significant predictors of adverse events, this does not necessarily go against Rushton’s principle of aggregation. Recall that the principle of aggregation states that the sum of a set of multiple measurements is a more stable and representative estimator than any single measurement. Significance of the predictive relationship between those measures and adverse events is not necessary in order for an average measurement to be a more stable and representative estimator than a single measurement. Because of the lack of findings for any of these relationships, we cannot directly determine from our study whether average psychosocial predictors were more representative than single measures but still not related to adverse events, or if our psychosocial measures were overall unrepresentative. Since the BDI and PSS are highly reliable and valid measures, this suggests that our negative findings may be valid in the case of depression and perceived stress. For major life events, obtained from our ad-hoc measure, it remains possible that our negative findings are not valid.

It is also interesting to note that for PSS, as well as BDI, mean scores in our sample steadily decreased between baseline and 3 months. As this implies that at least some participants were reporting less stress and depressive symptoms over the 3 month period, it begs us to consider whether or not the aggregation principle can be applied to all predictor variables analyzed in our study. The aggregation principle may apply most strongly to predictor variables that are relatively static over time. For variables such as PSS and BDI that decrease in the sample over time, perhaps a change score or computed regression slope for each individual would be a more appropriate predictor variable than an average score. This approach is discussed in more detail below as it relates to previous findings in the literature with the KCCQ.

Looking specifically at the standard heart failure predictors analyzed, the significance of BNP as a predictor of first adverse events in HF patients is consistent with the literature establishing BNP as a useful marker for prognosis in HF (25). Increases in BNP have corresponded to an increased risk of acute clinical heart failure decompensation (ADHF) events (which includes: cardiovascular death, admission for decompensated HF, or clinical HF decompensation requiring either parenteral HF therapy or changes in oral HF medications) (48). Moreover, as previously noted, the somewhat higher hazard ratios using average BNP assessments as opposed to single BNP assessments shows that repeated BNP measurements may further increase the predictive power of this biomarker in projecting adverse events.

Our significant findings for several KCCQ measures are consistent with the literature in showing that the KCCQ can predict risk of adverse events (33; 43; 52; 59). Previously, one study found that the KCCQ was associated with a higher short-term risk for new hospitalization for heart failure, independent of level of renal function and other known HF risk factors, in a population with chronic kidney disease (52). With a mean follow-up 4.3±1.6 years (0.7 – 6.7 years), the follow-up periods in this study and the present study were comparable. Interestingly, another study from Kosiborod and colleagues found that although a single measurement of KCCQ may be prognostic, additional predictive power can be obtained using change scores derived from repeated KCCQ assessments over 14 months of follow-up (43). The authors of this study found that adjusted analyses using 1-month KCCQ overall score were not predictive of all-cause mortality but did predict combined cardiovascular death and hospitalization (43). However, change score from 1 month to 3 month assessments significantly predict both all-cause mortality and the combined outcome of cardiovascular death and hospitalization (43). These findings were reproduced using a KCCQ change score from 3- and 6-month visits (43). Although the present study did not employ change scores, the overall consistency of average KCCQ measures in predicting adverse events relative to single KCCQ measures is in line with Kosiborod et al.'s findings.

Our results also showed that KCCQ better reflected time to first adverse event than NYHA classification or 6-MWT and is consistent with the existing literature (78). Given that the majority of our study's sample was African American, it is interesting to note that another study did not find any significant differences in KCCQ overall scores between non-Hispanic African Americans and non-Hispanic Caucasian heart failure patients (63). If KCCQ scores are consistent across African Americans and Caucasians, this may explain why the predictive validity of the KCCQ has been replicated in numerous studies with different sample characteristics. One recent study was found that was somewhat inconsistent with the present study; the authors concluded that lower KCCQ scores predicted mortality (Exp(B)=1.85; 95 % CI 1.16-2.95), but did not predict hospital admissions risk over a follow-up of 3.3 years (15). In examining the study's methods and sample characteristics, it is unclear what may have caused the differences in findings. The study had an older average sample age (69.1 years) than other studies in the literature, but also found that the prognostic power of the KCCQ score was consistent regardless of age (15).

While our findings do not support the 6-MWT as a predictor of time to first adverse event, other studies have shown a link between 6-MWT and adverse events in HF. One prior study showed that a higher risk of mortality or hospitalization for cardiovascular reasons was predicted by a 6-MWT distance of ≤ 468 m, with a hazard ratio of 2.77 (95% CI: 1.30-5.88) at one year and 1.71 (95% CI: 1.08-2.72) at three years in men with stable systolic heart failure (85). Mean 6-MWT distance at baseline was 444 meters (SD=129) in this study (85). By contrast, the highest mean distance walked in our sample at any time point was 362.28 meters. This may indicate a higher level of disability in our sample. Further, while this study only examined men, 21.7% of participants in our study were female. In addition, our sample is also younger than the sample in a study that did find a relationship between 6-MWT and hospital readmission (80).

Study Limitations

This study is limited in that only one outcome – time to first adverse event – was considered, and did not examine the number of events during follow-up. In addition, we only analyzed cardiac events and death, but an unobserved relationship may exist with non-cardiac events. Furthermore, the sample used may not have been large enough to power our analyses of psychosocial predictors. Attendance to clinic visits was only required for a subset of study participants with reported high or low stress, leaving a slightly smaller sample size to draw upon for the standard predictor variables. As such, our average values for these predictors may not be as robust. The issue of sample size may have been of most concern with the psychosocial variables for perceived stress, depression, and major life events.

While our study did look at multiple psychosocial variables and cardiovascular event risk, it did not examine the complex interactions between these psychosocial variables. We considered it beyond the scope of the present study to directly test the "perfect storm hypothesis" (3). This hypothesis postulates that amplified risk will occur in those with concurrent stress and depressive symptoms (3). For example, we did not evaluate whether individuals with high stress and low depressive symptoms and individuals with low stress and high depressive symptoms are at a decreased risk of adverse events as compared to individuals with both high stress and high depressive symptoms. Finally, we did not directly test in a single model whether average measures were stronger predictors than single measures; however, this could be examined in future research.

STUDY STRENGTHS

By targeting heart failure patients, our study is able to shed light on a population that is one of the most susceptible to hospitalization and rehospitalization in the United States. Given the significant economic impact of heart failure, our findings may inform improvements in the way heart failure is managed. Employing a novel longitudinal study design including multiple assessments over a long term period of 36 months, we are able to both examine the long-term impact of psychosocial and standard predictors on adverse events and compare the predictive advantage of single versus average measures. As more individuals with heart failure are living longer, it is becoming increasingly important to examine risk factors during long-term follow-up.

CLINICAL IMPLICATIONS

Our findings suggest that there may be limited utility to using multiple measures from the perceived stress scale, major life events checklist, and BDI in predicting event-free survival over a long-term maximum follow-up of 36 months. As strong predictors of event-free survival, baseline creatinine and single and multiple measures of KCCQ and BNP may be more informative risk factors for clinicians. For these predictors, we did find some evidence for the increased utility of using multiple measures in order to better predict outcomes. Given the time and resources required to administer multiple assessments to patients over time, the latter observation may inform what is the most practical and cost-effective schedule for risk assessment.

FUTURE DIRECTIONS

Future analyses should examine additional outcomes beyond time to first adverse event, such as number of adverse events and the incidence of non-heart failure hospitalizations. Potential outcomes could include duration of first hospitalization and number of total hospitalizations in long-term follow-up. Future studies should also examine differences between mild and major depression on adverse event outcomes. For long-term follow-up of adverse events, the predictive value of a life event scale may be increased if participants are asked to recall events over a longer span of time, such as 12 months, rather than 2 weeks. Positive and negative life events may be examined separately. The role of these events in exacerbating disease onset versus adverse events post-disease progression should be elucidated. Further, ecological momentary assessment or at-home online assessments may be better predictors, particularly for psychosocial assessments, in order to increase the number of assessments and response rate over the course of long-term follow-up. Another issue to consider is whether using change scores (which incorporate scores at two time points) or linear regression coefficients (which incorporate changes in scores from multiple time points), rather than average score, can enhance the predictive value of psychosocial and standard risk markers.

In sum, our study found that no single or average psychosocial variables were predictive of event-free survival, but all single and average BNP measures and multiple single and average KCCQ measures were predictive of event-free survival. With adjusted analyses finding only two of six single KCCQ measures as significant predictors, but eight of nine average KCCQ measures as significant predictors, there may be some evidence to support the hypothesis that multiple measures are stronger predictors than single measures.

Figures

Figure 1: Research Design for Time to Adverse Events

Baseline Visit N=144	Asmt 1	Asmt 2	Asmt 3	Asmt 4	Asmt 5	3 Month Visit N=106	6 Month Visit	12 Month Visit	18 Month Visit	24 Month Visit	30 Month Visit	36 Month Visit
Clinic	Phone Clinic	Phone Clinic	Phone Clinic	Phone Clinic	Phone Clinic	Clinic	Phone	Phone	Phone	Phone	Phone	Phone

Figure Note: PA = Phone Assessment; Asmt = Assessment

Figure 2: Graphical representation of BETRHEART study design

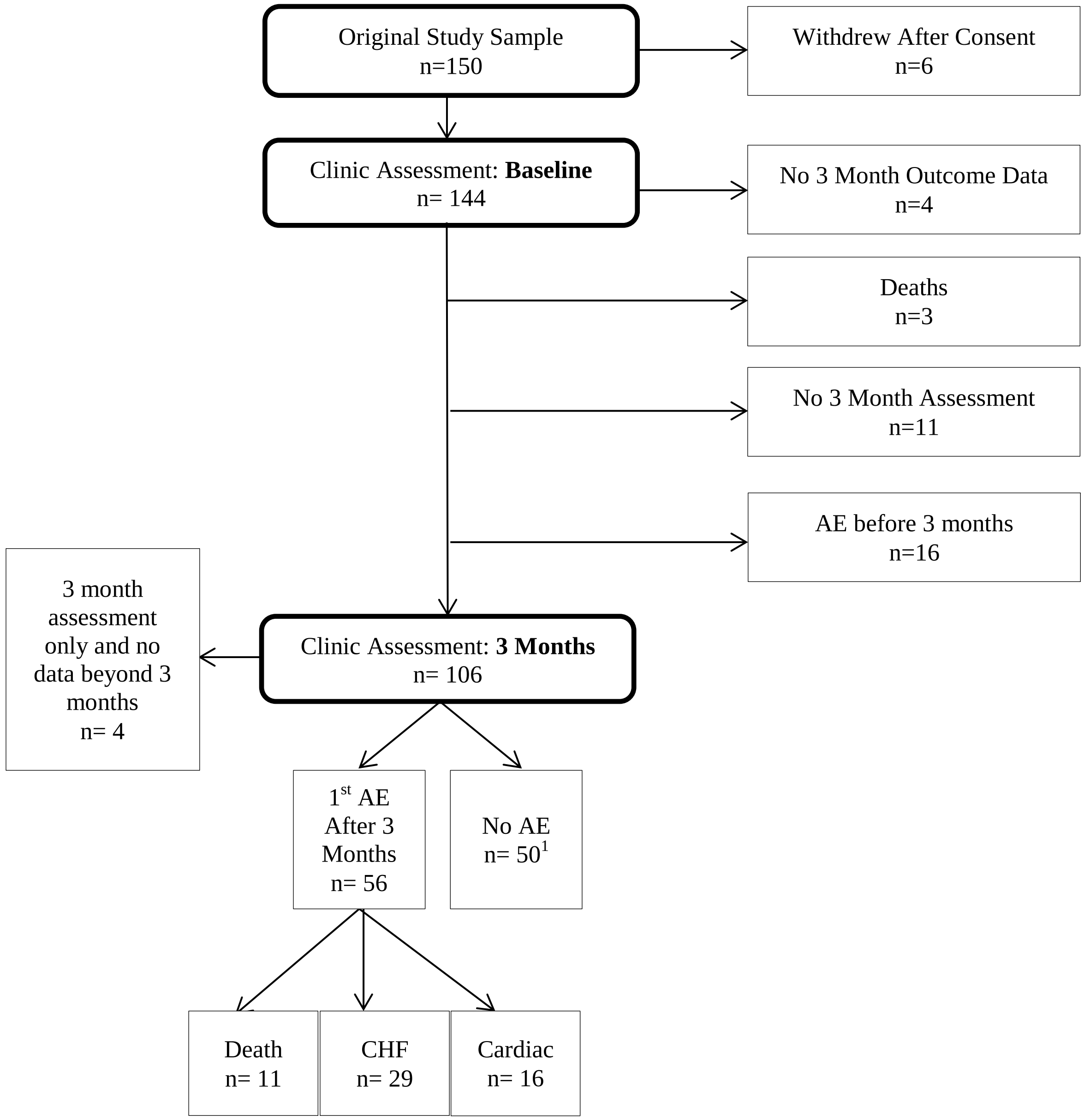

Figure note: AE=Adverse Event (includes CHF or Cardiac Hospitalization and Death); [1]Of those participants in our study who did not have any AEs before and after 3 months, 23 completed the full 36 months of the study, 18 withdrew or were lost to contact before 30 months, 8 completed only up to 30 months of the study, and 1 participant completed the 36 month assessment but did not respond to the 30 month assessment

Figure 3: Kaplan-Meier Curve for BDI at 3 Months and First Adverse Events (N=106)*

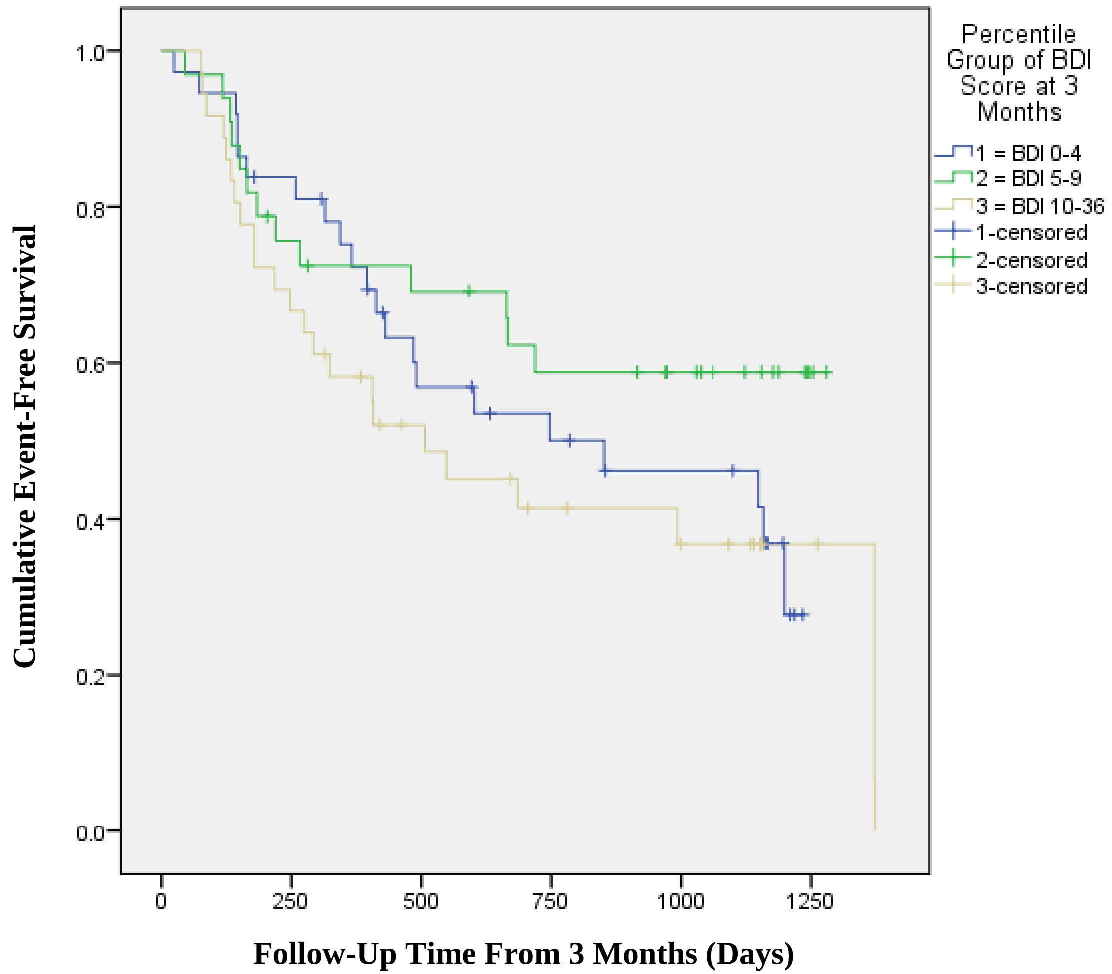

Figure Note: *Log Rank (Mantel-Cox) Chi Square = 3.407 (df=2, *p* = .182)

Figure 4: Kaplan-Meier Curve for BDI Average and First Adverse Events (N=106)*

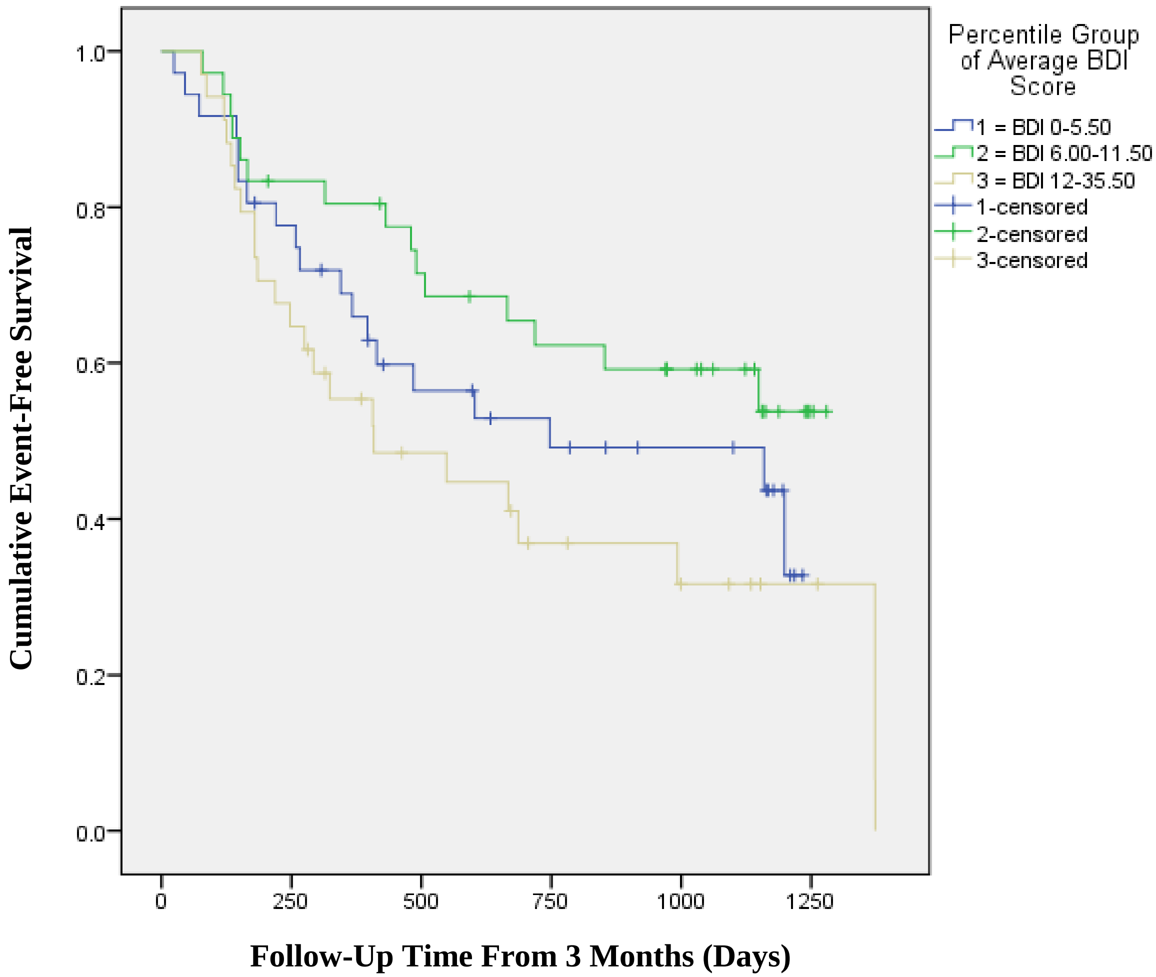

Figure Note: *Log Rank (Mantel-Cox) Chi Square = 4.894 (df=2, *p* = .087)

Figure 5: Kaplan-Meier Curve for PSS at 3 Months and First Adverse Events (N=106)*

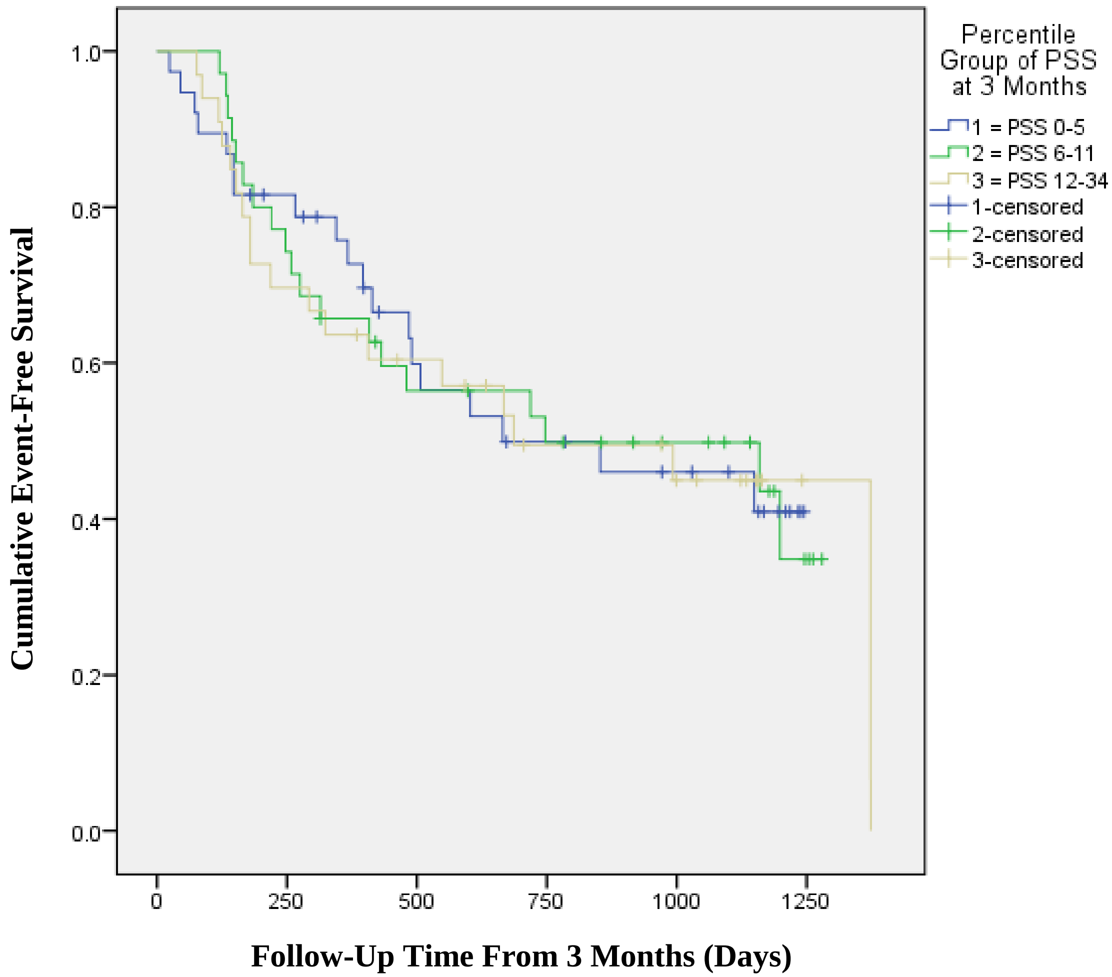

Figure Note: *Log Rank (Mantel-Cox) Chi Square = .014 (df=2, p = .993)

Figure 6: Kaplan-Meier Curve for PSS PA Average and First Adverse Events (N=106)*

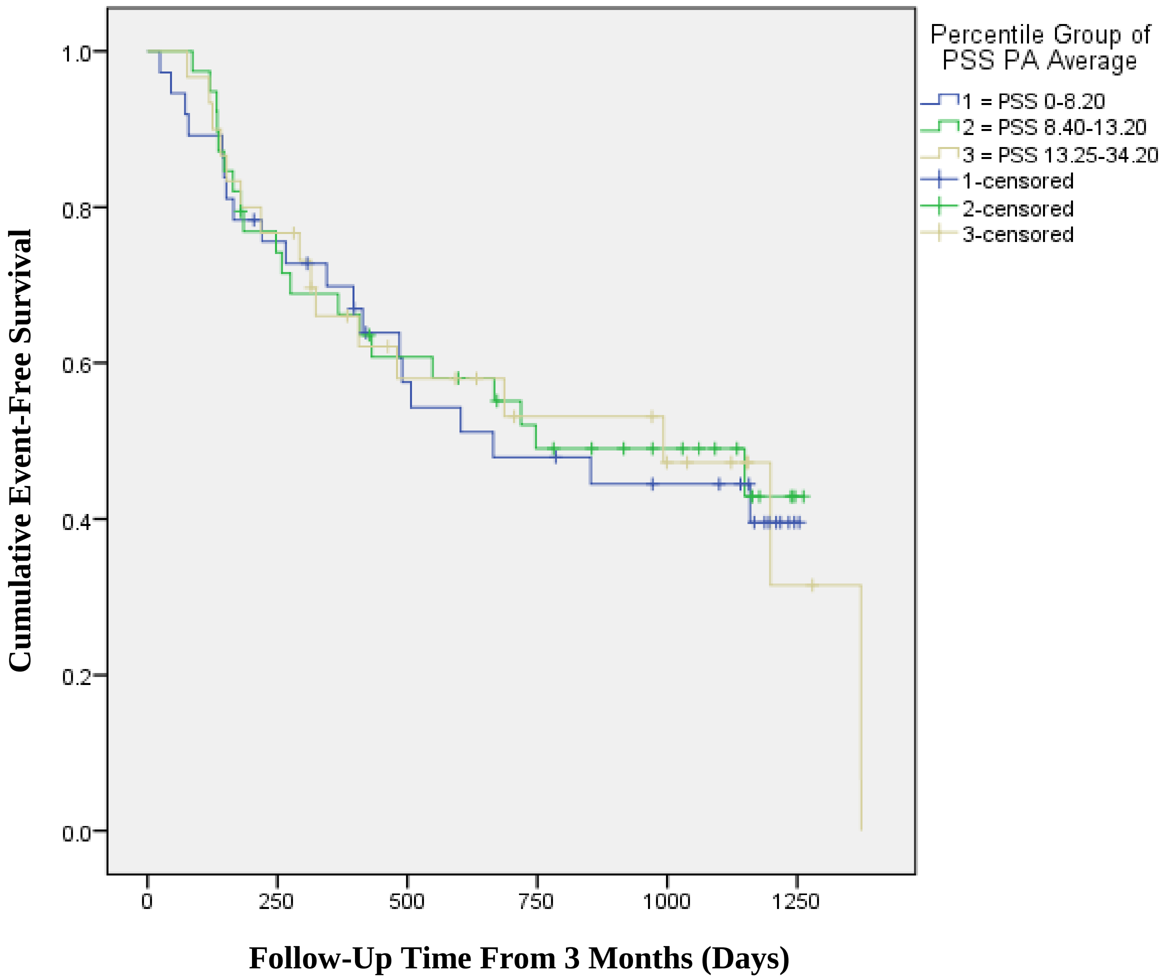

Figure Note: *Log Rank (Mantel-Cox) Chi Square = .061 (df=2, p = .970)

Figure 7: Kaplan-Meier Curve for KCCQ Overall Score at 3 Months and First Adverse Events (N=106)*

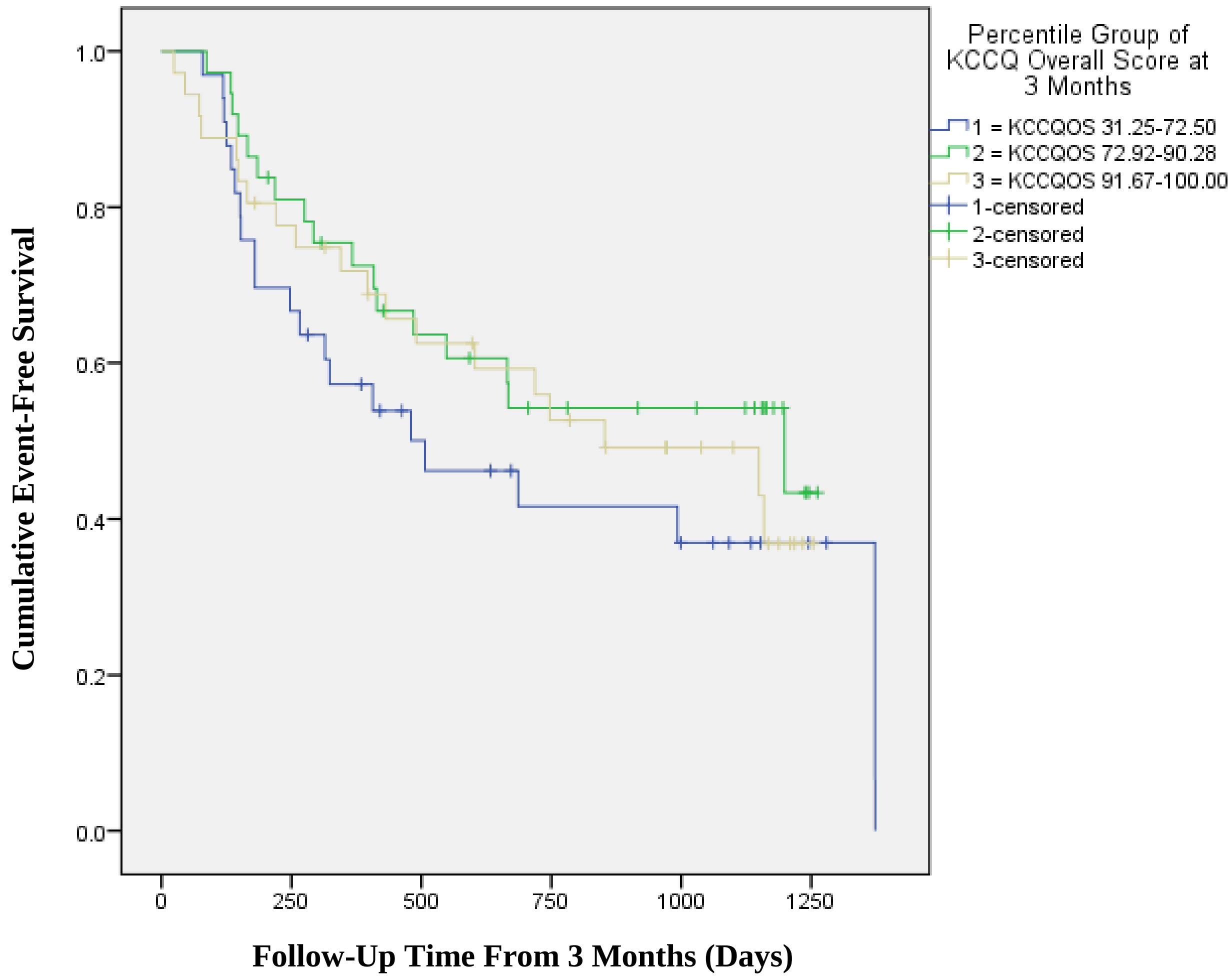

Figure Note: *Log Rank (Mantel-Cox) Chi Square = 1.865 (df=2, p = .394)

Figure 8: Kaplan-Meier Curve for KCCQ Overall Score All Visit Average and First Adverse Events (N=106)*

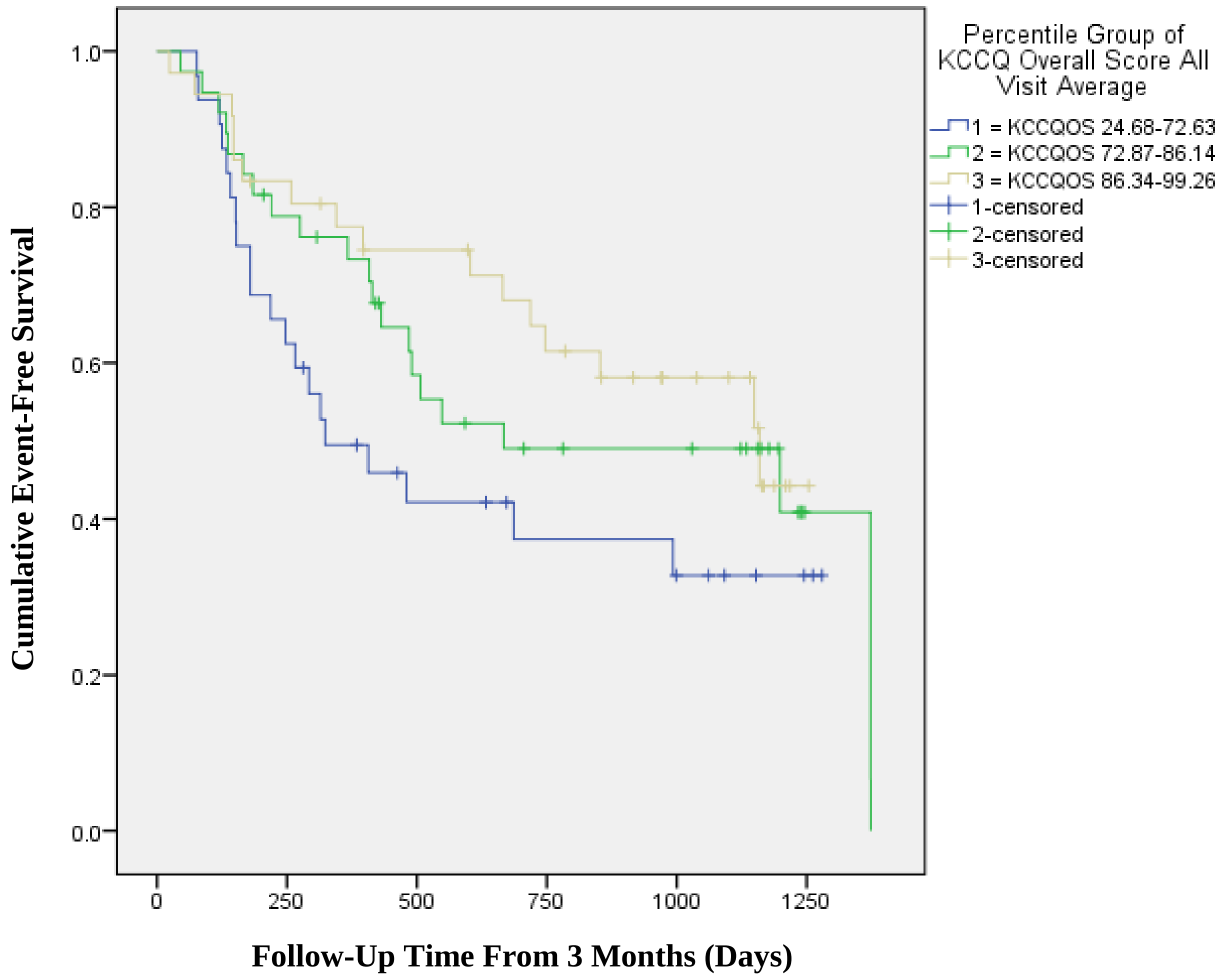

Figure Note: *Log Rank (Mantel-Cox) Chi Square = 4.168 (df=2, p = .124)

Figure 9: Kaplan-Meier Curve for lnBNP at 3 Months and First Adverse Events (N=106)*

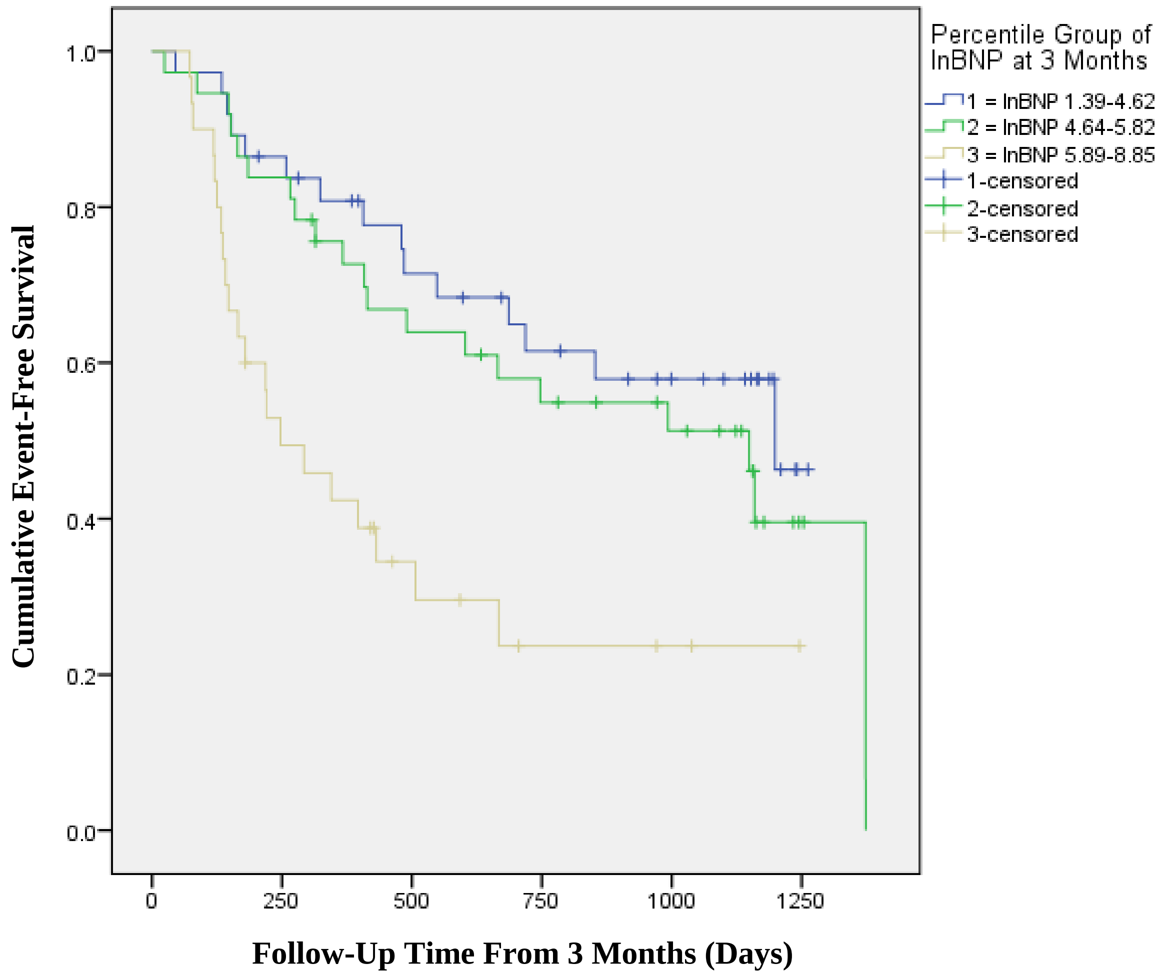

Figure Note: *Log Rank (Mantel-Cox) Chi Square = 14.372 (df=2, p = .001)

Figure 10: Kaplan-Meier Curve for lnBNP All Visit Average and First Adverse Events (N=106)*

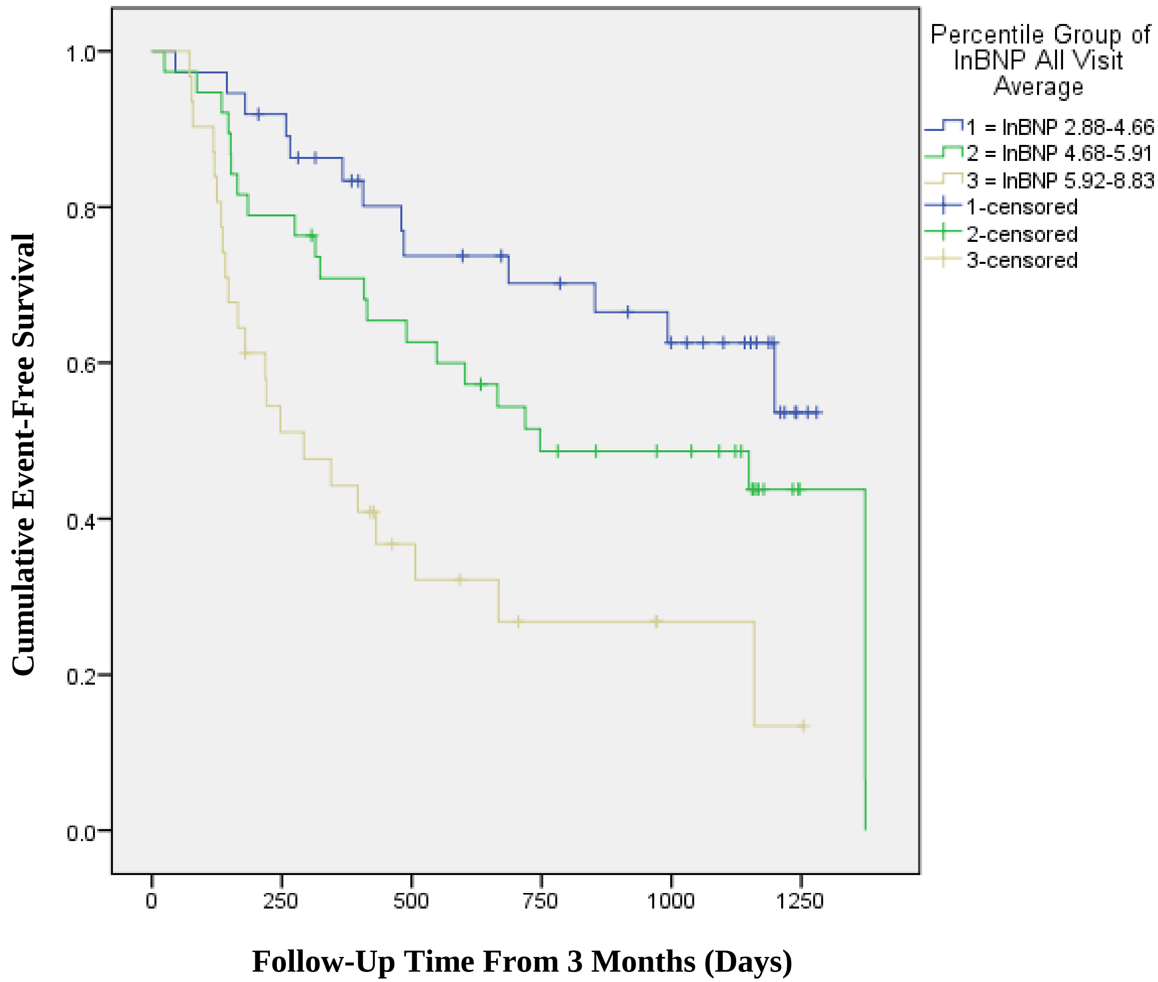

Figure Note: *Log Rank (Mantel-Cox) Chi Square = 16.069 (df=2, p = .000)

Tables

Table 1: Summary Statistics for Covariates for of Sample (N=106)

Variable	N	Mean/%	Std Dev	Median	Minimum	Maximum
BMI	106	31.71	7.85		17.85	52.31
Age	106	57.64	10.46		34.24	81.96
Gender	106					
Male	83	78.3%				
Female	23	21.7%				
Income	105*					
<15K	37	34.9%				
15-30K	29	27.4%				
30-70K	31	29.2%				
>70K	9	8.5%				
NYHA Class	106					
2	64	60.4%				
3	41	38.7%				
4	1	0.9%				

Ejection Fraction	106	22.74	7.38		5	40
Creatinine	103*	1.33	0.43		0.72	3.43
Hypertension	106					
Yes	83	78.3%				
No	23	21.7%				
Time to Event (Days)						
Participants with AE After 3 Months	56	52.8%	323.13	207.50	24	1373
Participants with No AE After 3 Months	50	47.2%	343.31	1049.50	179	1279
Total Sample	106	100%	423.92	747	24	1373

Table

Note: BMI = Body Mass Index; NYHA = New York Heart Association classification (data range from 2-4); *Missing data was imputed using the mean value for the sample such that all participants (N = 106) had data in final analyses.

Table 2: Summary Statistics for Additional Sociodemographic and Clinical Characteristics for Sample (N=106)

Variable	N	%
Race		
Caucasian	31	29.2%
African American	74	69.8%
American Indian/Alaska Native	1	0.9%
Ethnicity		
Not Hispanic/Latino	105	99.1%
Hispanic/Latino	1	0.9%
History of Smoking		
Yes (%)	76	71.7%
No (%)	30	28.3%
Employment Status		
Full time (%)	16	15.1%
Part time (%)	7	6.6%
Disabled (%)	59	55.7%
Unemployed (%)	1	0.9%
Retired (%)	23	21.7%

Table 3: Summary Statistics for Predictor Variables for Sample

Variable	N	Mean	Std Dev	Minimum	Maximum
PSS Baseline	106	12.85	8.11	0	32
PSS PA1	105	11.50	7.93	0	35
PSS PA2	101	11.87	8.10	0	40
PSS PA3	105	10.30	6.91	0	32
PSS PA4	103	11.04	7.41	0	40
PSS PA5	103	9.874	7.50	0	38
PSS 3-Months	106	9.76	7.97	0	34
PSS PA Average	106	10.96	6.30	0	34.20
BDI Baseline	106	11.68	9.13	0	39
BDI 3-Months	106	8.67	7.49	0	36
BDI Average	106	10.18	7.84	0	35.50
MLE Baseline	104	1.45	1.21	0	5
MLE PA1	102	1.41	1.34	0	6
MLE PA2	100	1.16	1.18	0	4
MLE PA3	105	1.10	1.21	0	6
MLE PA4	103	.971	1.03	0	5
MLE PA5	104	.904	1.08	0	5
MLE 3-Months	105	1.04	1.18	0	5
MLE PA Average	106	1.11	.795	0	3.60

Table 4: Correlation Matrix for Predictor Variables for Sample (N=106)

Variable	PSS Baseline	PSS 3-Months	PSS PA Average	MLE Baseline	MLE 3-Months	MLE PA Average	BDI Baseline	BDI 3-Months	BDI Average
PSS Baseline	1								
PSS-3 Months	.565**	1							
PSS PA Average	.699**	.846**	1						
MLE Baseline	.350**	.160	.280**	1					
MLE 3-Months	.121	.232*	.200*	.323**	1				
MLE PA Average	.325**	.291**	.418**	.571**	.468**	1			
BDI Baseline	.710**	.632**	.717**	.245*	.113	.338**	1		
BDI 3-Months	.619**	.670**	.660**	.123	.232*	.239*	.775**	1	
BDI Average	.710**	.689**	.733**	.201*	.177	.311**	.953**	.930**	1

Table Note: Data shown are Pearson's r. Ns vary from 103-106; *p < .05; **p < .01

Table 5: Results of Survival Analyses (N=106)

Predictor Variable	Covariates	PE	SE	HR	95% CI	p value
BDI Baseline	Unadjusted	.008	.014	1.008	.980-1.037	.565
	Adjusted	-.002	.015	.998	.969-1.028	.899
BDI 3-Months	Unadjusted	.020	.018	1.020	.985-1.057	.266
	Adjusted	.016	.019	1.016	.978-1.056	.408
BDI Average	Unadjusted	.015	.017	1.015	.981-1.050	.387
	Adjusted	.005	.018	1.005	.970-1.042	.770
PSS Baseline	Unadjusted	-.001	.017	.999	.967-1.033	.961
	Adjusted	.010	.017	1.010	.977-1.045	.552
PSS 3-Months	Unadjusted	.007	.017	1.007	.975-1.041	.660
	Adjusted	.006	.016	1.006	.974-1.039	.726
PSS PA Average	Unadjusted	.007	.021	1.007	.967-1.048	.752
	Adjusted	.006	.019	1.006	.969-1.045	.741
MLE Baseline	Unadjusted	-.069	.111	.934	.752-1.160	.534
	Adjusted	-.072	.122	.930	.733-1.181	.553
MLE 3-Months	Unadjusted	-.196	.124	.822	.644-1.048	.113
	Adjusted	-.243	.132	.784	.650-1.016	.066
MLE PA Average	Unadjusted	-.086	.169	.917	.658-1.278	.610
	Adjusted	-.107	.175	.898	.637-1.267	.541

Table Note: PSS = Perceived Stress Scale; PA = Phone Assessment; Adjusted = adjusted for age, gender, BMI, income, NYHA, hypertension, ejection fraction, creatinine; BDI = Beck Depression Inventory; MLE = Major Life Events; PE = Parameter Estimate for Cox Proportional Hazards Regression; SE = Standard Error; HR = Hazard Ratio CI = Confidence Interval. Each predictor variable was tested in a separate model.

Table 6: Example Adjusted Survival Analysis with Covariates (N=106)

Covariate	PE	SE	HR	95% CI	p value
Gender	-.436	.411	.647	.289-1.447	.289
Hypertension History	.361	.388	1.434	.670-3.071	.353
NYHA Class	.381	.280	1.464	.846-2.534	.173
Ejection Fraction	.000	.020	1.000	.962-1.040	.353
Age at Baseline	.023	.015	1.023	.993-1.054	.129
BMI	-.001	.022	.966	.957-1.043	.966
Creatinine	1.060	.329	2.888	1.515-5.505	.001
Income	.019	.156	1.019	.750-1.384	.966
PSS PA Average	.006	.019	1.006	.969-1.045	.741

Table Note: PSS = Perceived Stress Scale; PA = Phone Assessment; PE = Parameter Estimate for Cox Proportional Hazards Regression; SE = Standard Error; HR = Hazard Ratio CI = Confidence Interval. Each predictor variable was tested in a separate model; For gender, which was coded either as 1 or 2, 2 = Female and 1 = Male.

Table 7: Correlation Matrix for KCCQ Variables (N=106)

Variable	KCCQ Overall Summary Score Baseline	KCCQ Symptom Burden Score Baseline	KCCQ Total Symptom Score Baseline	KCCQ Overall Summary Score 3-Months	KCCQ Symptom Burden Score 3-Months	KCCQ Total Symptom Score 3-Months	KCCQ Overall Summary Score Baseline and 3-Month Average	KCCQ Symptom Burden Score Baseline and 3-Month Average	KCCQ Total Symptom Score Baseline and 3-Month Average	KCCQ Overall Summary Score Clinic Visit Average	KCCQ Symptom Burden Score Clinic Visit Average	KCCQ Total Symptom Score Clinic Visit Average	KCCQ Overall Summary Score All Visit Average	KCCQ Symptom Burden Score All Visit Average	KCCQ Total Symptom Score All Visit Average
KCCQ Overall Summary Score Baseline	1														
KCCQ Symptom Burden Score Baseline	.839**	1													
KCCQ Total Symptom Score Baseline	.854**.	.942**	1												
KCCQ Overall Summary Score 3-Months	686**	.510**	.554**	1											
KCCQ Symptom Burden Score 3-Months	.621**	.520**	.555**	.793**	1										
KCCQ Total Symptom Score 3-Months	.642**	.521**	.601**	.813**	.929**	1									
KCCQ Overall Summary Score Baseline and 3-Month Average	.932**	.750**	.781**	.903**	.762**	.784**	1								
KCCQ Symptom Burden Score Baseline and 3-Month Average	.852**	.905**	.885**	.725**	.834**	.800**	.864**	1							
KCCQ Total Symptom Score	.846**	.839**	.914**	.750**	.810**	.874**.	.873**	.945**	1						

Baseline and 3-Month Average															
KCCQ Overall Summary Score Clinic Visit Average	.788**	.579**	.620**	.839**	.742**	.773**	.884**	.750**	.772**	1					
KCCQ Symptom Burden Score Clinic Visit Average	.609**	.543**	.568**	.748**	.797**	.816**	.733**	.754**	.763**	.860**	1				
KCCQ Total Symptom Score Clinic Visit Average	.634**	.544**	.616**	.745**	.762**	.838**	.746**	.737**	.803**	.873**	.957**	1			
KCCQ Overall Summary Score All Visit Average	.876**	.678**	.718**	.893**	.771**	.799**	.962**	.822**	.842**	.976**	.826**	.840**	1		
KCCQ Symptom Burden Score All Visit Average	.762**	.751**	.754**	.782**	.869**	.851**	.839**	.918**	.891**	.866**	.950**	.916**	.878**	1	
KCCQ Total Symptom Score All Visit Average	.769**	.710**	.787**	.789**	.826**	.895**	.847**	.871**	.933**	.873**	.917**	.960**	.890**	.954**	1

Table Note: Data shown are Pearson's r. Ns vary from 103-106; *p < .05; **p < .01

Table 8: Results of Survival Analyses with KCCQ as a Predictor

Predictor Variable	N	Covariates	PE	SE	HR	95% CI	p value
KCCQ Overall Summary Score Baseline	106	Unadjusted	-.013	.007	.987	.974-1.001	.066
		Adjusted	-.016	.008	.984	.969-.999	.042*
KCCQ Symptom Burden Score Baseline	106	Unadjusted	-.012	.005	.988	.978-.998	.021*
		Adjusted	-.013	.006	.987	.975-.999	.030*
KCCQ Total Symptom Score Baseline	106	Unadjusted	-.013	.006	.987	.976-.999	.027*
		Adjusted	-.012	.007	.988	.975-1.002	.086
KCCQ Overall Summary Score 3-Months	106	Unadjusted	-.014	.008	.986	.970-1.002	.085
		Adjusted	-.018	.010	.982	.964-1.001	.058
KCCQ Symptom Burden Score 3-Months	106	Unadjusted	-.010	.007	.990	.976-1.004	.148
		Adjusted	-.013	.008	.987	.973-1.002	.096
KCCQ Total Symptom	106	Unadjusted	-.010	.007	.990	.976-1.004	.159

Score 3-Months							
		Adjusted	-.009	.008	.991	.975-1.007	.261
KCCQ Overall Summary Score Baseline and 3-Month Average	106	Unadjusted	-.016	.008	.984	.968-1.00	.049*
		Adjusted	-.021	.009	.980	.962-.998	.029*
KCCQ Symptom Burden Score Baseline and 3-Month Average	106	Unadjusted	-.016	.007	.984	..970-.998	.024*
		Adjusted	-.019	.008	.982	.966-.997	.022*
KCCQ Total Symptom Score Baseline and 3-Month Average	106	Unadjusted	-.016	.007	.985	.970-.999	.035*
		Adjusted	-.014	.009	.986	.969-1.003	.099
KCCQ Overall Summary Score Clinic Visit Average	101	Unadjusted	-.022	.008	.978	.963-.993	.005**
		Adjusted	-.025	.009	.976	.958-.993	.007**
KCCQ Symptom Burden Score Clinic Visit Average	101	Unadjusted	-.018	.007	.982	.969-.996	.013*

		Adjusted	-.022	.008	.978	.963-.994	.007**
KCCQ Total Symptom Score Clinic Visit Average	101	Unadjusted	-.017	.007	.983	.970-.997	.017*
		Adjusted	-.019	.008	.981	.965-.997	.023*
KCCQ Overall Summary Score All Visit Average	106	Unadjusted	-.020	.008	.980	.964-.996	.013*
		Adjusted	-.025	.010	.976	.958-.994	.010*
KCCQ Symptom Burden Score All Visit Average	106	Unadjusted	-.019	.007	.98	.967-.995	.009**
		Adjusted	-.024	.009	.977	.960-.993	.005**
KCCQ Total Symptom Score All Visit Average	106	Unadjusted	-.018	.007	.982	.968-.996	.015*
		Adjusted	-.019	.009	.981	.964-.998	.030*

Table Note: KCCQ = Kansas City Cardiomyopathy Questionnaire; Adjusted = adjusted for age, gender, BMI, income, NYHA, hypertension, ejection fraction, creatinine; PE = Parameter Estimate for Cox Proportional Hazards Regression; SE = Standard Error; HR = Hazard Ratio CI = Confidence Interval. Each predictor variable was tested in a separate model. *p < .05

Table 9: Results of Survival Analyses with BNP as a Predictor (N=106)

Predictor Variable	N	Covariates	PE	SE	HR	95% CI	p value
lnBNP Baseline	105	Unadjusted	.492	.136	1.636	1.254-2.134	.000**
		Adjusted	.464	.156	1.590	1.172-2.157	.003**
lnBNP 3-Months	104	Unadjusted	.466	.105	1.594	1.297-1.958	.000**
		Adjusted	.423	.131	1.527	1.181-1.974	.001**
lnBNP Baseline and 3-Month Average	106	Unadjusted	.544	.126	1.723	1.347-2.205	.000**
		Adjusted	.502	.153	1.652	1.224-2.229	.001**
lnBNP Clinic Visit Average Only	100	Unadjusted	.488	.124	1.629	1.278-2.076	.000**
		Adjusted	.526	.162	1.692	1.233-2.323	.001**
lnBNP Baseline, Clinic Visit, and 3-Month Average	106	Unadjusted	.560	.126	1.750	1.366-2.241	.000**
		Adjusted	.574	.163	1.775	1.290-2.442	.000**

Table Note: ln = natural log; BNP = Brain/B-Type Natriuretic Peptide; Adjusted = adjusted for age, gender, BMI, income, NYHA, hypertension, ejection fraction, creatinine; PE = Parameter Estimate for Cox Proportional Hazards Regression; SE = Standard Error; HR = Hazard Ratio CI = Confidence Interval. Each predictor variable was tested in a separate model. *p < .05, **p < .01

Table 10: Results of Survival Analyses with 6-Minute Walk Test as a Predictor (N=106)

Predictor Variable	**N**	**Covariates**	**PE**	**SE**	**HR**	**95% CI**	**p value**
6-MWT Baseline	96	Unadjusted	-.001	.001	.999	.998-1.000	.104
		Adjusted	.000	.001	1.000	.999-1.002	.828
6-MWT 3-Months	94	Unadjusted	-.001	.001	.999	.998-1.000	.041*
		Adjusted	-.001	.001	.999	.998-1.000	.155
6-MWT Baseline and 3-Month Average	102	Unadjusted	-.001	.001	.999	.998-1.000	.026*
		Adjusted	-.001	.001	.999	.998-1.001	.435
6-MWT Clinic Visit Average	95	Unadjusted	-.001	.001	.999	.998-1.000	.029*
		Adjusted	-.001	.001	.999	.998-1.001	.261
6-MWT Baseline, Clinic Visit, and 3-Month Average	104	Unadjusted	-.001	.001	.999	.998-1.000	.026*
		Adjusted	-.001	.001	.999	.998-1.001	.340

Table Note: 6-MWT = 6-Minute Walk Test (outcome: total distance in feet walked); Adjusted = adjusted for age, gender, BMI, income, NYHA, hypertension, ejection fraction, creatinine; PE = Parameter Estimate for Cox Proportional Hazards Regression; SE = Standard Error; HR = Hazard Ratio CI = Confidence Interval. Each predictor variable was tested in a separate model. *p < .05

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